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Comparison of immediate and long-term outcomes in men and women undergoing revascularisation for chronic limb threatening ischaemia (CLTI) in the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1) trial

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Short title: Benson et al. Sex differences and outcomes in the BASIL-1 trial

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What does this study/review add to the existing literature and how will it influence future clinical practice:

Existing data comparing men and women after revascularisation have all been extrapolated from retrospective cohort studies or national registries. The anatomical and clinical disease severity within the datasets, treatment decisions and length of follow up is heterogeneous and therefore difficult to draw reliable conclusions from. This study is the first to compare outcomes for men and women in a randomised setting. It suggests that for infrainguinal disease, men are in fact worse off than women after limb salvage procedures in the long term.

Key Words: Critical limb ischaemia; Chronic limb threatening ischaemia; Peripheral vascular disease; Infrainguinal bypass; Angioplasty; Sex.

Abstract

Background: The reports from cohort studies comparing outcomes after revascularisation for chronic limb threatening ischaemia (CLTI) between men and women remains controversial. Anatomical and clinical disease severity is often heterogeneous, and treatment choice influenced by a variety of clinician and patient factors. Our aim was to compare outcomes in men and women entered into the only randomised study comparing bypass and angioplasty for infra-inguinal disease causing severe limb ischaemia.

Methods: Data were obtained from BASIL-1 trial case record forms. Baseline demographics were compared, and Cox proportional hazard models were used to examine the relationship between sex and amputation free survival (AFS), overall survival (OS), and freedom from major adverse limb events (FF-MALE) using a per-protocol analysis. Data was analysed using a per-protocol analysis.

Results: 452 patients were randomized into the BASIL-1 from 1999-2004. At randomisation, women were older and less likely to be smokers, to have diabetes, or to be on recommended best medical therapy. Men were more likely to present with gangrene. Ankle brachial pressure index (ABPI), post-revascularisation length of hospital stay, and 30-day morbidity and mortality were similar for men and women. At 3 years, female sex was associated with significantly better AFS (HR 0.65, 95% CI 0.47-0.89, p=<0.01), OS (HR 0.66 95% CI 0.46-0.95, p=0.02) and FF-MALE (HR 0.74, 95% CI 0.57-0.96, p=0.02).

Conclusion: In the BASIL-1 trial, women had similar short-term, but better long-term outcomes after revascularisation. Sex is an important consideration when developing early, evidence-based treatment pathway and revascularisation strategies for CLTI, and is an independent risk factor for outcomes following revascularisation as well as development of symptomatic PAD.

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Introduction

Due to ageing populations, smoking, and diabetes, chronic limb threatening ischaemia (CLTI) secondary to peripheral arterial disease (PAD) is an increasing global healthcare issue (1). CLTI is the leading cause of limb loss, and an important cause of premature mortality, worldwide (2). Although excess mortality has been reported in women suffering from other vascular conditions, such as acute myocardial infarction (MI) and ruptured abdominal aortic aneurysm (3–5), the influence of sex on outcomes following revascularisation specifically for CLTI remains poorly defined. Thus, studies comparing men and women often fail to clearly distinguish those with claudication or CLTI. The majority of CLTI studies exclude sex as a significant co-variate, in part due to the relatively small number of women included, and the results of those that do are contradictory (6–11). It is generally accepted that women presenting with CLTI tend to be significantly older and less likely to be smokers than their male counterparts (12). A disadvantage of cohort studies is their inability to assess for any possible impact of clinician bias and/or patient choice on decisions regarding open or endovascular revascularisation. Endovascular procedures are linked to shorter lengths of stay and fewer immediate complications, therefore often selected in patients with higher burdens of co-morbidity. This bias has implications for outcome reporting in a non-randomised setting.

The UK NIHR HTA-funded Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial remains the only randomised controlled trial (RCT) to have compared bypass surgery (BS) first and balloon angioplasty (BA) first revascularisation strategies for CLTI (13). The BASIL trial dataset offers a unique opportunity to examine the impact of sex on outcomes following surgical and endovascular infra-inguinal revascularisation for CLTI, in a randomised cohort. The aim of this study was to investigate the effect of sex on immediate and long-term major adverse limb events (MALE), amputation free survival (AFS) and

overall survival for men and women after treatment out to 3 years. Secondary aims were to compare incidence of cumulative re-intervention at 1 and 3 years following the primary intervention.

Methods

The BASIL-1 trial:

The BASIL-1 trial methods have been published previously in detail(14). Ethical approval was obtained from the Multi-Centre Research Ethics Committee for Scotland. Briefly, between August 1999 and June 2004, 452 patients presenting to 27 UK hospitals with CLTI due to infra-inguinal disease were randomised to a BS or BA first revascularisation strategy. Patients were followed up to death or study end date. All surviving patients had a minimum of 3 years of follow-up.

Definitions of Variables:

An ex-smoker was defined as some-one who reported that they had not smoked for at least one year. Post-revascularisation morbidity was defined as major (above ankle) amputation, myocardial infarction, cerebrovascular event, haematoma, infection (wound, chest, urinary tract) or false aneurysm within 30-days.

Endpoints:

All analyses were performed based on the treatment received. Amputation free survival (AFS) was defined as freedom from (above ankle) amputation or death from any cause. Re-intervention was defined as any surgical bypass, angioplasty or ‘other surgical’ (non-bypass) intervention on the index limb following primary intervention (this did not include major amputation). Overall survival (OS) was defined as freedom from death from any cause. Major adverse limb events (MALE) were defined as freedom from major amputation (transtibial or above) or any major vascular reintervention such as thrombectomy or revision of a failed graft in the index limb during the follow-up period. Time to event was taken as the

date of the first event. Cox proportional hazard models were used to examine the relationship between sex and AFS, OS and MALE whilst adjusting for age, clinical presentation, ankle to brachial pressure index (ABPI), and the type of revascularisation received. Time to event analyses were presented using Kaplan-Meier plots. Analysis was performed using SAS (version 9.4).

Results

The analysis included a total of 433 patients who underwent BA or BS as their first procedure after randomisation. This cohort comprised 257 men (128 BS, 129 BA) and 176 women (67 BS and 109 BA). Baseline characteristics of men and women are shown in **Table 1**. Women were older at randomization (74.2 vs 71.8, $p \leq 0.01$) and less likely to be smokers (36% of women denied ever having smoked vs only 9% of men, $p \leq 0.01$). They were also more likely to have untreated hypercholesterolaemia (15% of women vs 9% of men) and less likely to be on an anti-platelet agent (56% vs 61% of men), although the differences were non-significant. Rates of insulin dependent diabetes were similar, although men were more likely to suffer from non-insulin dependent diabetes. Baseline creatinine was significantly higher in men (123 ± 97 μmol/L vs 102 ± 45 μmol/L, $p \leq 0.01$). Although baseline ABPI were similar in men and women, men were more likely to have a diagnosis of gangrene ($p \leq 0.05$). Baseline mobility was similar. However more men had an existing diagnosis of PAD at randomisation (19% vs 13% of women), and 17% vs 12% of women had already undergone a procedure in the trial leg.

At 30-days, there was no difference in post-procedural morbidity (33% versus 29%), mortality (4% vs 3%) or length of hospital stay. Although women showed a trend towards shorter hospital stays (median LOS 11 [IQR 4-21] vs 15 [IQR 7-26]) negative binomial model estimates failed to demonstrate an association. As expected, patients who underwent surgical bypass spent longer in hospital (IRR 1.71[1.36-2.13] p=<0.01), as well as those presenting with tissue loss (2.08 [1.69-2.56], p=<0.01).

Table 2 shows the number of cumulative re-interventions at 1 and 3 year follow-up for men and women after their primary intervention. Overall, rates of re-intervention in men and women were similar. At 1 year, 27% of men and 26% of women had required further re-

intervention, and at 3-years 32% had undergone re-intervention in both groups. Logistic regression models failed to find any significant factors affecting need for re-intervention including sex, primary intervention or severity of clinical presentation.

However after 3 years, women were found to have a significantly better AFS (HR 0.65, CI 0.47, 0.89, p=<0.01) (Figure 1), OS (HR 0.66 (0.4634, 0.9487), p=0.02) (Figure 2) and MALE (HR 0.74 (0.57, 0.96), p=0.02) (Figure 3). Assessment for differences in treatment effect for sex was not statistically significant (p=0.2 at 3 year follow up).

Discussion

Our findings add to previously published studies focusing on short term outcomes, either survival to discharge or 30-day morbidity and mortality. Those studies often include a more heterogenous population e.g. a mix of mild and severe limb ischaemia or claudicants and CLTI, with differing anatomical patterns, and do not use ABPI values to classify presence of critical ischaemia. Therefore the advantages of the BASIL cohort remains its well described inclusion criteria of patients with CLTI, requiring infra-inguinal treatment. Although ABPI was not part of the study inclusion criteria, values were available for inclusion in the analysis. Although women were significantly older than men, with differing risk factor profiles at presentation, the incidence of 30-day post-revascularisation morbidity and mortality were similar to men, with better AFS, OS and MALE at long term follow up,. This fits with non-randomised studies which have also noticed similar patterns of poorer outcomes for men in the longer term (out to five years) related to higher incidence of cardiovascular related death for equivalent optimisation(15). Our findings suggest that the deviation in outcomes begins at between 1 and 3 years. It also suggests that post-intervention outcomes are influenced heavily by factors already present at the point of presentation. If we wish to improve on the disparities seen between men and women, we need to target epidemiological differences in the community at the earliest manifestations of symptoms.

Although haemodynamic severity of disease (ABPI) was similar men were more likely to present with gangrene or to have undergone a previous vascular intervention in the trial leg prior randomisation. This suggests men were more likely to be undergoing redo procedures. Redo surgery and the presence of tissue loss have previously been associated with worse peri-operative outcomes compared to primary procedures and patients with rest pain only(16,17). There are also likely to be major healthcare pathway differences between the BASIL population and cohorts described in other published non-UK national registries.

There is likely to be more than one factor influencing the impact of sex on outcomes after revascularisation. The randomised nature of the group allows us to remove one aspect of bias relating to surgical approach. We have shown several baseline characteristics that differ between the two groups, several of which are known to influence outcomes after revascularisation. This suggests that by the time patients undergo intervention for SLI, sex-based differences have already manifested themselves in the pre-operative care pathway. There is awareness that women with PAD are underdiagnosed or diagnosed later, with associated reductions in screening and management of associated risk factors(18).

Of note, 15/87 women (17%) randomised to receive bypass crossed over into the angioplasty group, compared to 7/141 men (5%). As patients were technically suitable for both strategies it could be hypothesised that baseline features led to a change in management. However this cannot be proven with the available data.

Although further research, including an analysis of data from on-going UK NIHR HTA funded RCTs such as BASIL 2(19) and 3(20), and BEST-CLI(21) will be required in order to more fully define the relationship between sex and outcome for CLTI, present data from the BASIL trial supports suggestions that sex is an important factor when considering evidence-based revascularisation strategies. Poorer pre-operative pathways for women, suggested here by reduced implementation and/or compliance with best medical therapy, indicate that there are further gains to be made in the optimisation of any patient in earlier stages of peripheral vascular disease.

Study Limitations: The trial recruited patients with rest pain or tissue loss, however an ankle pressure of <50mmHg was not a requirement. Therefore the population was more heterogeneous than a strict ‘critical limb ischaemia’ cohort. However, compared to large registry data, many of which do not include ABPI to classify CLI, we have been able to use ABPI in the modelling. Analysis of differences in sex for long-term outcomes was not in the

original BASIL protocol. Therefore, our findings are exploratory analyses used to generate future hypothesises relating to strategies to improve outcomes for all patients undergoing revascularisation for limb ischaemia. Finally, post-operative differences in anatomical appearances post treatment in the two groups was not analysed in the original trial. Therefore anatomical treatment success could not be included in the analysis.

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Disclosures: The authors have nothing to disclose

Conflicts of Interest: None

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